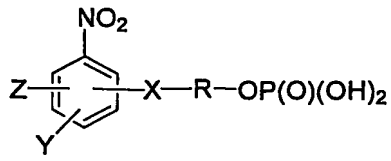
Claims

1. A phosphate compound of Formula (I)



(I)

wherein:

X represents at any available ring position –CONH-, -SO_2NH-, -O-, -CH_2-, -NHCO- or -$NHSO_2$-;

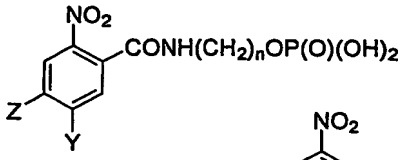
R represents a lower C_{1-6} alkyl optionally substituted with one or more groups including hydroxy, amino and N-oxides therefrom or dialkylamino and N-oxides therefrom;

Y represents at any available ring position -N-aziridinyl, -$N(CH_2CH_2W)_2$ or –$N(CH_2CHMeW)_2$, where each W is independently selected from halogen or -OSO_2Me.

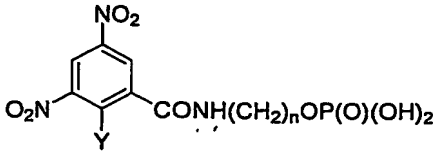
Z represents at any available ring position -NO_2, -halogen, -CN, -CF_3 or -SO_2Me;

and pharmaceutically acceptable salts and derivatives thereof.

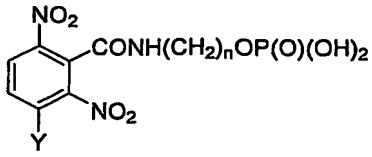
2. A phosphate compound of Formula (I) as claimed in claim 1 which is selected from a compound represented by formulae (Ia), (Ib) or (Ic)



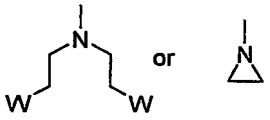
(Ia)



(Ib)



(Ic)

wherein Y represents  or

and wherein

n represents 1 to 6

Z represents $-NO_2$, -halogen, -CN, $-CF_3$ or $-SO_2Me$; and

where each W is independently selected from halogen or $-OSO_2Me$

and pharmaceutically acceptable salts and derivatives thereof.

3. The phosphate compound of Formula (I) as claimed in claim 1 or claim 2 which is selected from:

2-[[2-[Bis(2-bromoethyl)amino]-3,5-dinitrobenzoyl]amino]ethyl dihydrogen phosphate;

3-[[5-[Bis(2-chloroethyl)amino]-2,4-dinitrobenzoyl]amino]propyl dihydrogen phosphate;

3-[[5-[Bis(2-bromoethyl)amino]-2,4-dinitrobenzoyl]amino]propyl dihydrogen phosphate;

2-[[2-[Bis(2-chloroethyl)amino]-3,5-dinitrobenzoyl]amino]ethyl dihydrogen phosphate;

2-[(2-Chloroethyl)-2,4-dinitro-6-[[[2-(phosphonooxy)ethyl]amino]-carbonyl]anilino]ethyl methanesulfonate;

2-({2-[Bis(2-bromopropyl)amino]-3,5-dinitrobenzoyl}amino)ethyl dihydrogen phosphate;

2-[(2-Bromoethyl)-2,4-dinitro-6-[[[2-(phosphonooxy)ethyl]amino]-carbonyl]anilino]ethyl methanesulfonate;

2-[[2-[Bis(2-iodoethyl)amino]-3,5-dinitrobenzoyl]amino]ethyl dihydrogen phosphate ;

2-[(2-Iodoethyl)-2,4-dinitro-6-({[2-(phosphonooxy)ethyl]amino}carbonyl)-anilino]ethyl methanesulfonate;

2-[(2-Chloroethyl)-2,4-dinitro-3-[[[3-(phosphonooxy)propyl]amino]-carbonyl]anilino]ethyl methanesulfonate;

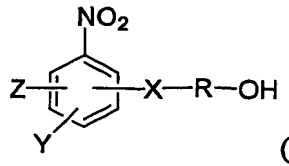
3-({3-[Bis(2-bromoethyl)amino]-2,6-dinitrobenzoyl}amino)propyl dihydrogen phosphate;

2-[(2-Bromoethyl)-2,4-dinitro-3-[[[2-(phosphonooxy)ethyl]amino]-carbonyl]anilino]ethyl methanesulfonate;

2-[(2-Bromoethyl)-2,4-dinitro-3-[[[3-(phosphonooxy)propyl]amino]-carbonyl]anilino]ethyl methanesulfonate; and

2-[(2-Iodoethyl)-2,4-dinitro-3-[[[3-(phosphonooxy)propyl]amino]-carbonyl]anilino]ethyl methanesulfonate.

4. An alcohol compound of Formula (II)



(II)

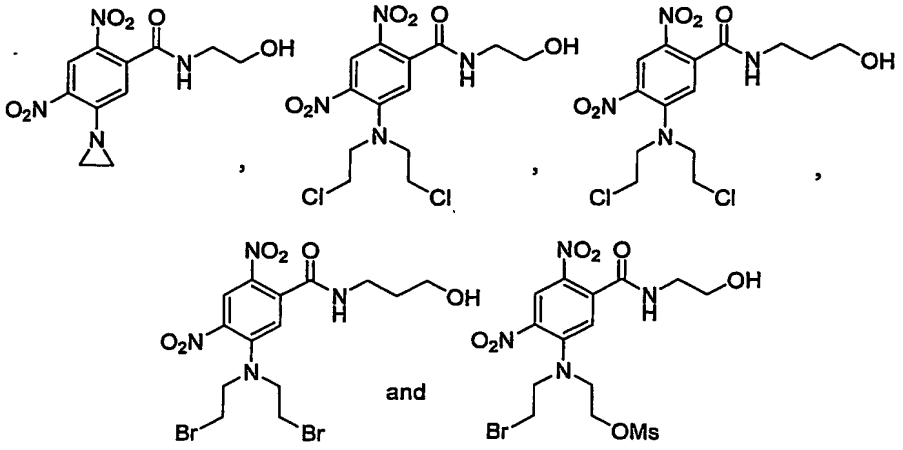
wherein:

X represents at any available ring position –CONH-, -SO_2NH-, -O-, -CH_2-, -NHCO- or -$NHSO_2$-;

Y represents at any available ring position -N-aziridinyl, -$N(CH_2CH_2W)_2$, or -$N(CH_2CH\,MeW)_2$ where each W is independently selected from halogen or -OSO_2Me;

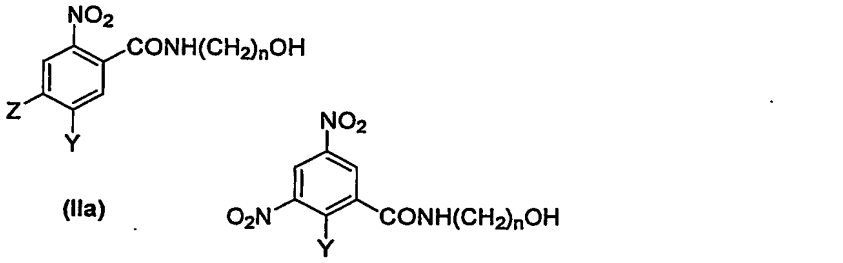
Z represents at any available ring position -NO_2, -halogen, -CN, -CF_3 or -SO_2Me;

R represents a lower C_{1-6} alkyl optionally substituted with one or more groups including hydroxy, amino and N-oxides therefrom or dialkylamino and N-oxides therefrom; and pharmaceutically acceptable salts and derivatives thereof, with the proviso that



are excluded.

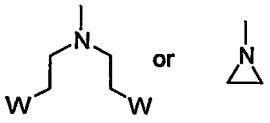
5. The alcohol compound of Formula (II) as claimed in claim 4 selected from a compound represented by formulae (IIa), (IIb) or (IIc)



(IIa)

(IIb)

(IIc)

wherein Y may represent  or

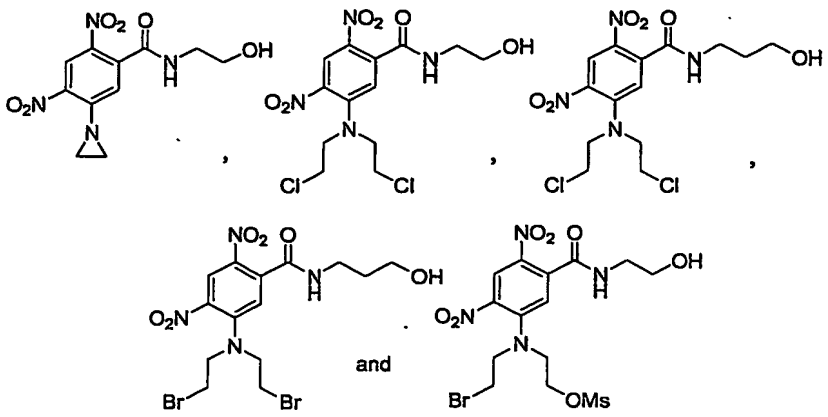
and wherein

n represents 1 to 6

Z represents $-NO_2$, -halogen, -CN, $-CF_3$ or $-SO_2Me$; and

where each W is independently selected from halogen or $-OSO_2Me$

and pharmaceutically acceptable salts and derivatives thereof with the proviso that



are excluded.

6. The alcohol compound of Formula (II) as defined in claim 5 selected from a compound of Formula (IIb) or (IIc) as defined in claim 5.

7. The alcohol compound of Formula (II) as defined in claim 5 or claim 6 selected from:

N-(3-Hydroxypropyl)-5-[bis(2-chloroethyl)amino]-2,4-dinitrobenzamide;

N-(3-Hydroxypropyl)-5-[bis(2-bromoethyl)amino]-2,4-dinitrobenzamide;

N-(2-Hydroxyethyl)-5-[bis(2-bromoethyl)amino]-2,4- dinitrobenzamide;

N-(4-Hydroxybutyl)-5-[bis(2-bromoethyl)amino]-2,4-dinitrobenzamide;

N-(5-Hydroxypentyl)-5-[bis(2-bromoethyl)amino]-2,4-dinitrobenzamide;

N-(6-Hydroxyhexyl)-5-[bis(2-bromoethyl)amino]-2,4-dinitrobenzamide;

5-[Bis(2-bromoethyl)amino]-N-(2-hydroxyethyl)-4-(methylsulfonyl)-2-nitrobenzamide;

2[(2-Bromoethyl)-5-[[(3-hydroxypropyl)amino]carbonyl]-2,4-dinitroanilino]ethyl methanesulfonate;

5-[Bis(2-iodoethyl)amino]-N-(2-hydroxyethyl)-2, 4-dinitrobenzamide;

2-[Bis(2-Chloroethyl)amino]-N-(2-hydroxyethyl)-3,5-dinitrobenzamide;

2-[Bis(2-bromoethyl)amino]-N-(2-hydroxyethyl)-3,5-dinitrobenzamide;

2-[Bis(2-chloroethyl)amino]-N-(3-hydroxypropyl)-3,5-dinitrobenzamide;

2-[Bis(2-bromoethyl)amino]-N-(3-hydroxypropyl)-3,5-dinitrobenzamide;

2-[Bis(2-chloroethyl)amino]-N-(4-hydroxybutyl)-3,5-dinitrobenzamide;

2-[Bis(2-bromoethyl)amino]-N-(4-hydroxybutyl)-3,5-dinitrobenzamide;

2-[Bis(2-chloroethyl)amino]-N-(5-hydroxypentyl)-3,5-dinitrobenzamide;

2-[Bis(2-bromoethyl)amino]-N-(5-hydroxypentyl)-3,5-dinitrobenzamide;

2-[Bis(2-chloroethyl)amino]-N-(6-hydroxyhexyl)-3,5-dinitrobenzamide;

2-[Bis(2-bromoethyl)amino]-N-(6-hydroxyhexyl)-3,5-dinitrobenzamide;

2-[Bis(2-bromopropyl)amino]-N-(2-hydroxyethyl)-3,5-dinitrobenzamide;

2-((2-Bromoethyl)-2-{[(2-hydroxypropyl)amino]carbonyl}-4,6-dinitroanilino)ethyl methanesulfonate;

2-((2-Bromoethyl)-2-{[(2-hydroxyethyl)amino]carbonyl}-4,6-dinitroanilino)ethyl methanesulfonate;

2-((2-Chloroethyl)-2-{[(2-hydroxyethyl)amino]carbonyl}-4,6-dinitroanilino)ethyl methanesulfonate;

2-[Bis(2-iodoethyl)amino]-N-(2-hydroxyethyl)-3,5-dinitrobenzamide;

2-((2-Iodoethyl)-2-{[(2-hydroxyethyl)amino]carbonyl}-4,6-dinitroanilino)ethyl methanesulfonate;

3-[Bis(2-bromoethyl)amino]-N-(2-hydroxyethyl)-2,6-dinitrobenzamide;

2-((2-Bromoethyl)-3-{[(2-hydroxyethyl)amino]carbonyl}-2,4-dinitroanilino)ethyl methanesulfonate;

3-[Bis(2-bromoethyl)amino]-N-(3-hydroxypropyl)-2,6-dinitrobenzamide;

2-((2-bromoethyl)-3-{[(3-hydroxypropyl)amino]carbonyl}-2,4-dinitroanilino)ethyl methanesulfonate;

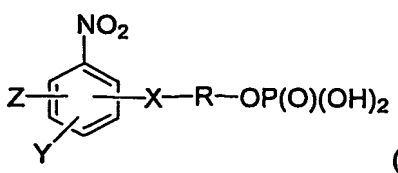
3-[Bis(2-bromoethyl)amino]-N-(4-hydroxybutyl)-2,6-dinitrobenzamide;

2-((2-Bromoethyl)-3-{[(4-hydroxybutyl)amino]carbonyl}-2,4-dinitroanilino)ethyl methanesulfonate;

2-((2-Chloroethyl)-3-{[(3-hydroxypropyl)amino]carbonyl}-2,4-dinitroanilino)ethyl methanesulfonate; and

2-((2-Iodoethyl)-3-{[(3-hydroxypropyl)amino]carbonyl}-2,4-dinitroanilino)ethyl methanesulfonate.

8. A method of preparing a phosphate represented by the general formula (I);



(I)

wherein:

X represents at any available ring position –CONH-, -SO_2NH-, -O-, -CH_2-, -NHCO- or -$NHSO_2$-;

R represents a lower C_{1-6} alkyl optionally substituted with one or more groups including hydroxy, amino and N-oxides therefrom or dialkylamino and N-oxides therefrom;

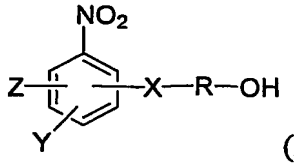
Y represents at any available ring position -N-aziridinyl or -$N(CH_2CH_2W)_2$, where each W is independently selected from halogen or -OSO_2Me;

Z represents at any available ring position -NO_2, -halogen, -CN, -CF_3 or -SO_2Me;

and pharmaceutically acceptable salts and derivatives thereof;

the method including the step of

(i) phosphorylating a compound of formula (II)



(II)

wherein:

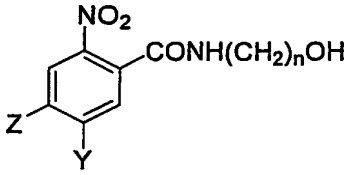
X represents at any available ring position –CONH-, -SO_2NH-, -O-, -CH_2-, -NHCO- or -$NHSO_2$-;

Y represents at any available ring position -N-aziridinyl, -$N(CH_2CH_2W)_2$, or -$N(CH_2CHMeW)_2$ where each W is independently selected from halogen or -OSO_2Me;

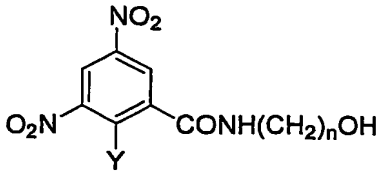
Z represents at any available ring position -NO_2, -halogen, -CN, -CF_3 or -SO_2Me; and

R represents a lower C_{1-6} alkyl optionally substituted with one or more groups including hydroxy, amino and N-oxides therefrom or dialkylamino and N-oxides therefrom.

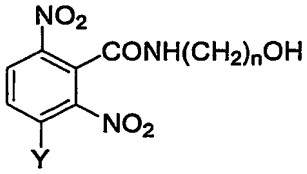
9. A method of preparing a compound of formulae (IIa), (IIb) or (IIc)



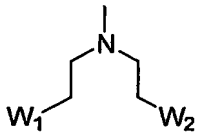
(IIa)



(IIb)



(IIc)

wherein Y may represent 

and wherein

n represents 1 to 6

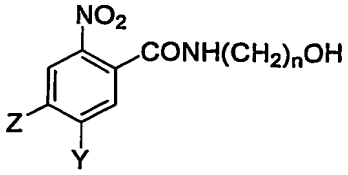
Z represents $-NO_2$, -halogen, -CN, $-CF_3$ or $-SO_2Me$; and

where W_1 is halogen and W_2 is $-OSO_2Me$

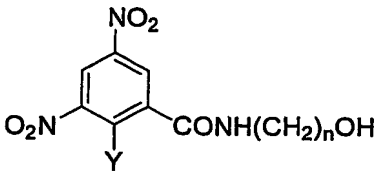
and pharmaceutically acceptable salts and derivatives thereof;

the method including the step of

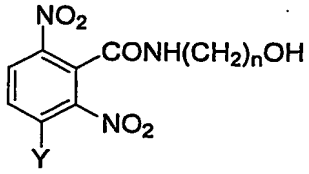
reacting a compound of formulae (IIa'), (IIb') or (IIc') optionally with heating



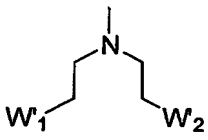
(IIa')



(IIb')



(IIc')

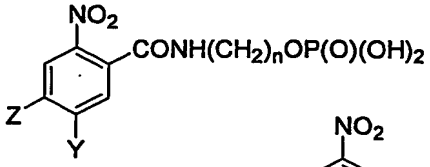
wherein Y may represent 

wherein W'_1 and W'_2 are each halogen;

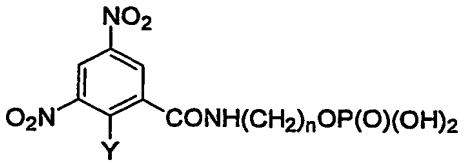
with an effective amount of silver methanesulfonate (AgOMs) in a solvent to give a compound of formulae (IIa), (IIb) or (IIc) defined above in this claim.

10. The method as claimed in claim 9 wherein the solvent is selected from MeCN or other polar non-protic solvent.

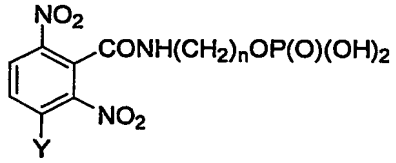
11. A method of preparing a compound of formulae (Ia), (Ib) or (Ic)



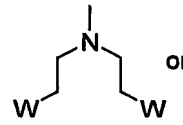
(Ia)



(Ib)



(Ic)

wherein Y may represent  or 

and wherein

n represents 1 to 6

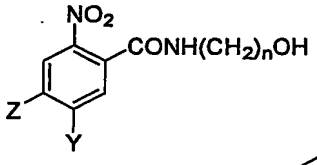
Z represents $-NO_2$, -halogen, -CN, $-CF_3$ or $-SO_2Me$; and

where each W is independently selected from halogen or $-OSO_2Me$

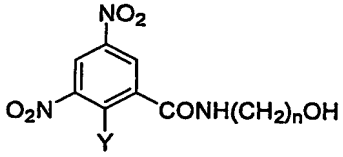
and pharmaceutically acceptable salts and derivatives thereof

the method including the step of

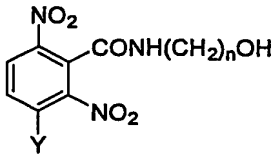
phosphorylating a compound represented by formulae (IIa), (IIb) or (IIc)



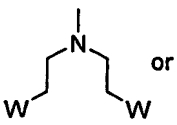
(IIa)



(IIb)



(IIc)

wherein Y represents  or 

and wherein

n represents 1 to 6

Z represents $-NO_2$, -halogen, -CN, $-CF_3$ or $-SO_2Me$; and

where each W is independently selected from halogen or $-OSO_2Me$

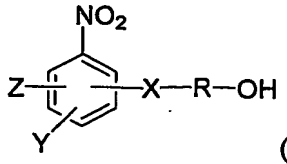
and pharmaceutically acceptable salts and derivatives.

12. A compound of formula (I) when obtained by the method defined in claim 8.

13. A compound of formula (Ia), (Ib) or (Ic) when obtained by the method defined in claim 11.

14. A compound of formula (IIa), (IIb) or (IIc) obtained by the method defined in claim 9 or claim 10.

15. A method of cell ablation utilising at least one nitroreductase enzyme including the step of administering a compound of Formula (I) as defined above in any one of claims 1 to 3 or a compound of Formula (II)



(II)

wherein:

X represents at any available ring position –CONH-, $-SO_2NH-$, -O-, $-CH_2-$, -NHCO- or $-NHSO_2-$;

Y represents at any available ring position -N-aziridinyl, $-N(CH_2CH_2W)_2$, or $-N(CH_2CHMeW)_2$ where each W is independently selected from halogen or $-OSO_2Me$;

Z represents at any available ring position $-NO_2$, -halogen, -CN, $-CF_3$ or $-SO_2Me$;

R represents a lower C_{1-6} alkyl optionally substituted with one or more groups including hydroxy, amino and N-oxides therefrom or dialkylamino and N-oxides therefrom; and pharmaceutically acceptable salts and derivatives thereof;

or a mixture thereof in an effective amount to ablate cells wherein said cells express at least one nitroreductase enzyme.

16. The method as claimed in claim 15 wherein the at least one nitroreductase enzyme is encoded for by the nfsB gene of either *E. coli* or by orthologous genes in *Clostridia* species.

17. The method as claimed in claim 15 or claim 16 wherein the cell ablation provides a substantially minimal bystander effect.

18. The method as claimed in any one of claims 15 to 17 wherein the cells that express the at least one nitroreductase enzyme are tumour cells in tissue in a subject.

19. The method as claimed in any one of claims 15 to 18 wherein the cell ablation is achieved through GDEPT (gene-directed enzyme-prodrug therapy).

20. The method as claimed in any one of claims 15 to 19 wherein the cell ablation is achieved through ADEPT (antibody-directed enzyme-prodrug therapy).

21. The method as claimed in any one of claims 15 to 20 wherein the cells are mammalian.

22. A method of providing anticancer therapy, wherein a compound of Formula (I) as defined above in any one of claims 1 to 3 is administered in a therapeutically effective amount to tumour cells in a subject.

23. The method as claimed in claim 22 wherein the therapeutically effective amount administered is between about 20% to 100% of the maximum tolerated dose of said subject.

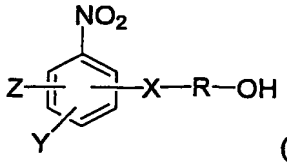
24. The method as claimed in claim 21 or claim 22 wherein the compound of Formula (I) or Formula (II) is administered for use in cell ablation in conjunction with at least one nitroreductase enzyme.

25. The method as claimed in claim 24 wherein the cell ablation is achieved through GDEPT (gene-directed enzyme-prodrug therapy) or ADEPT (antibody-directed enzyme prodrug therapy).

26. The method as claimed in claim 24 or claim 25 wherein the at least one nitroreductase enzyme is encoded for by the nfsB gene of either *E. coli* or by orthologous genes in *Clostridia* species.

27. The method as claimed in any one of claims 21 to 26 including the further step of irradiating the tumour cells.

28. A pharmaceutical composition including a therapeutically effective amount of a compound of Formula (I) as defined in any one of claims 1 to 3 or a compound of Formula (II)



(II)

wherein:

X represents at any available ring position –CONH-, -SO_2NH-, -O-, -CH_2-, -NHCO- or -$NHSO_2$-;

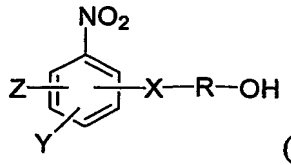
Y represents at any available ring position -N-aziridinyl, -N($CH_2CH_2W)_2$ or -N(CH_2CH MeW)$_2$, where each W is independently selected from halogen or -OSO_2Me;

Z represents at any available ring position -NO_2, -halogen, -CN, -CF_3 or -SO_2Me;

R represents a lower C_{1-6} alkyl optionally substituted with one or more groups including hydroxy, amino and N-oxides therefrom or dialkylamino and N-oxides therefrom; and pharmaceutically acceptable salts and derivatives thereof,

or a mixture thereof, and a pharmaceutically acceptable excipient, adjuvant, carrier, buffer or stabiliser.

29. The use in the manufacture of a medicament of an effective amount of a compound of Formula (I) as defined in any one of claims 1 to 3 or a compound of Formula (II)



(II)

wherein:

X represents at any available ring position –CONH-, $-SO_2NH-$, -O-, $-CH_2-$, -NHCO- or $-NHSO_2-$;

Y represents at any available ring position -N-aziridinyl, $-N(CH_2CH_2W)_2$ or $-N(CH_2CHMeW)_2$, where each W is independently selected from halogen or $-OSO_2Me$;

Z represents at any available ring position $-NO_2$, -halogen, -CN, $-CF_3$ or $-SO_2Me$;

R represents a lower C_{1-6} alkyl optionally substituted with one or more groups including hydroxy, amino and N-oxides therefrom or dialkylamino and N-oxides therefrom; and pharmaceutically acceptable salts and derivatives thereof, or mixtures thereof, to ablate cells that express at least one nitroreductase enzyme.

30. The use as claimed in claim 29 wherein the medicament is further adapted for GDEPT (gene-directed enzyme-prodrug therapy) or ADEPT (antibody-directed enzyme therapy).

31. The use as claimed in claim 29 or claim 30 wherein the at least one nitroreductase enzyme is encoded for by the nfsB gene of either *E. coli* or by orthologous genes in *Clostridia* species.

32. The use as claimed in any one of claims 29 to 31 wherein the medicament is adapted to ablate target cells with a substantially minimal bystander effect.

33. The use as claimed in any one of claims 29 to 31 wherein the medicament is adapted for mammalian cells.